disclose how to provide data on biological activity or bioavailability, and no references disclosing this type of analysis had been cited.

Applicants submit that it is well within the ability of one of ordinary skill in the art to obtain data on biological activity or bioavailability. Indeed, tests for biological activity may be as simple as providing the compound to a laboratory test animal and observing the results. Bioavailability may be assessed by dissolution in an acidic solution, as reflected in the U.S. Pharmacopeia. The dissolution test procedure measures the rate at which a compound dissolves while stirred in an acidic solution. A copy of that test procedure is provided herewith.

Rejection of Claims 1-55 Under 35 U.S.C. §112, second paragraph

Claims 1-55 were rejected under 35 U.S.C. §112, second paragraph, as being indefinite for various reasons. First, claim 1 was rejected because the Office Action asserted that the language "a method of searching for possible forms of a sample" was unclear. The Office Action asserted that "a method for detecting possible forms" was more appropriate.

Applicants submit that the Office Action should allow Applicants discretion in choosing appropriate terms. "The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. 112, second paragraph is whether the claim meets the threshold requirements of clarity and precision, not whether more suitable language or modes of expression are available." MPEP, §2173.02 (8th Ed. 2001) (emphasis added). Furthermore, Applicants submit that "method for searching" is actually more appropriate than "method for detecting", because the claimed method includes solidifying a sample as well as detecting its form. The term "searching" is a more accurate description of what is being done.

Next, the Office Action rejected claims 1 and 34 because they recite "forms" of a sample, which was said to be an indefinite term. Applicants submit that "forms" has a plain and ordinary meaning in the art that is recognizable to one of ordinary skill based on the present application. As explained in the present application, "[t]he form of a compound or mixture refers to the arrangement of molecules in the solid." (Application, page 14, lines 27-29). A compound or mixture may be arranged in a crystalline state, where the molecules exist in fixed conformations and are arranged in a regular way. "When a compound has different solid or crystalline forms, the different forms are frequently referred to as polymorphs of the compound." (Application page 3, lines 10-13). Indeed, as the Office Action later acknowledges, the prior art has recognized the existence of different forms of a compound. "Gu teaches characterization of polymorphic forms of the sample using FT-Raman spectroscopy." (Office Action, page 7, paragraph 14). Thus, the specification makes the term "form" clear and recognizable.

Claim 12 was rejected as indefinite because the word "placing" had not been used in the parent claim, and it was allegedly unclear how the sample could be placed into a block or sheet. Applicants have amended claim 12 so that it refers to the "disposing" step of claim 1. As to the second point, Applicants submit that a sample may be placed in a block or sheet by placing the sample in the holes or pores of the block or sheet.

Claim 21 was rejected because it recites "at least one different form of the sample." Claim 21 has been amended to clarify that at least one form is generated that is different than a known form of the sample. The amendment is supported by the application, for example, at page 11, lines 12-16.

Claims 26 and 27 were rejected as unclear, and the Office Action asked what it meant that the centrifuging is sufficient to facilitate in-situ analysis or to provide environmental

variation. Applicants submit that these claims are clear in the context of the present application. The application states, "First, centrifuging may assist evaporation or concentrate solid or semisolid material at one end of a capillary space. This has advantages in connection with in-situ analysis, in that the generated form will be located at a consistent place in the receptacle." (Application, page 20, lines 28-32). Thus, it is clear that centrifuging must be sufficient to locate the generated solids at a consistent place in the receptacle. With respect to environmental variation, centrifuging two or more samples at different speeds or for different lengths of time will provide environmental variation, which is desirable in a screening method.

Claim 53 was rejected because it recites "a method of screening a sample." The Office Action stated that it was unclear how it is possible to screen just one sample. The Office Action also stated that "at least one form" and "generated form" did not have antecedent basis in the claim. Applicants have amended claim 53 to correct the lack of antecedent basis. Claim 53 now requires analyzing the solids in the capillary tubes in a manner wherein the analytical result is indicative of form, and classifying the solids according to form. This amendment also answers the Office Action's questions, "how it is possible to screen just one sample? What is it screened for?" The sample is divided into several capillary tubes, and solids are generated in those capillary tubes. A variety of forms may be found in the capillary tubes. Thus, the sample is screened according to form.

Claim 54 was rejected as incomplete. The Office Action stated that "said centrifuging step at least partially" was unclear. Applicants submit that the Office Action has incorrectly parsed the claim. Claim 54 reads:

> 54. The method of claim 53, wherein said centrifuging step is at least partially during said solidifying step.

Claim 54 requires that at least part of the centrifuging step occurs during the solidifying step; in other words, the centrifuging step can start before and/or continue after the solidifying step, but there must be some overlap between the centrifuging step and the solidifying step.

Applicants submit that the foregoing amendments and remarks overcome the rejections of the claims based on 35 U.S.C. §112, second paragraph. Applicants request that the rejections be withdrawn.

General Response To Prior Art Rejections

Claims 1-40, 42-53 and 55 were rejected on various prior art grounds. Applicants believe those rejections are based on a misunderstanding of the nature of the present methods, particularly as to the "forms" involved. Applicants have explained the meaning of forms above, and provide the following general comments.

The present application relates to novel methods of searching for different forms of a compound and screening a compound according to its forms. The present methods require solidifying the sample in one or more capillary spaces, such as capillary tubes. The methods also require analyzing the solids in a manner wherein the analytical result is indicative of the form of the solid, and classifying the solid according to form. These methods are based on the surprising discovery that novel forms are more likely to be generated and detected by solidifying samples in capillary spaces. None of the prior art references discloses searching for or screening by forms in this fashion, as discussed in more detail below.

The Office Action appears to misunderstand the nature of the present methods. The Office Action appears to believe the present methods are simply crystallization methods that use capillary tubes. (See, for example the rejections based on Hol and Plaas-Link). To the contrary,

the present application acknowledges that capillary tubes have been previously used for crystallization. (See page 7, lines 19-28). However, there has been no recognition that one was more likely to obtain a variety of different forms by conducting a number of crystallizations in capillaries. Applicants submit that the rejected claims require more than crystallizing in capillary tubes and therefore are not anticipated or rendered by such crystallizations.

Rejection of Claims 1-3, 6-9, 11, 13, 14, 20, 21, 34-37, 39, 40, 42, 43, 45 and 50-52 Under 35 U.S.C. §102(e) Based On Hol et al. U.S. Patent No. 6,267,935 B1

Claims 1-3, 6-9, 11, 13, 14, 20, 21, 34-37, 39, 40, 42, 43, 45, and 50-52 were rejected as anticipated by Hol et al. U.S. Patent No. 6,267,935 B1. According to the Office Action, Hol teaches a method for screening different crystalline and amorphous forms of biologically active macromolecules. The conditions are varied to obtain crystal forms instead of amorphous forms for some of the compounds. The Office Action states, "The conditions are varied to obtain crystal forms instead of amorphous forms for some of the compounds." (Page 4, paragraph 4).

Applicants respectfully submit that the Office Action is in error. The Office Action erroneously states that Hol teaches varying conditions to obtain different forms. Hol does not indicate any or desire to obtain a variety of solid forms. Indeed, the Office Action later recognizes this by stating, "Hol, Plaas-Link and Schuler do not teach Raman spectroscopic analysis in their methods or discuss polymorphic forms of the compounds." (Office Action, page 7, paragraph 14) (emphasis added).

Hol provides Crystallization Solution Sets that might be used to crystallize proteins. Hol asserts that some of its solutions can be used to crystallize proteins that have been recalcitrant to crystallization. Thus, Hol's concern is to obtain crystals suitable for three-dimensional structure

determination. Hol is not concerned with obtaining different forms of those proteins. Indeed, Hol does not even show a consciousness of the possibility that different forms of a compound might be obtained. Hol does not indicate that amorphous solids are a desired result, since it refers to its alleged invention as "Crystallization Solution Sets."

Although Hol discloses that capillary tubes might be used for crystallization, it is not Hol's preferred technique for crystallization. Instead, Hol prefers the vapor diffusion crystallization technique. (column 9, lines 55-61). Further, Hol does not disclose a difference in crystallization results arising from the use of different techniques for the crystallization. To the contrary, Hol indicates that, if one wishes to obtain better crystals, the pH and temperature should be adjusted, not the type of receptacle or the technique used for crystallization. (column 11, lines 21-26).

For the foregoing reasons, Applicants submit that the rejection of claims 1-3, 6-9, 11, 13, 14, 20, 21, 34-37, 39, 40, 42, 43, 45, and 50-52 based on Hol is improper and should be withdrawn.

Rejection of Claims 1, 2, 8, 9, 11, 13, 17, 18, 20, 34, 36, 39, 40, 42, 45, 48 and 49 Under 35 U.S.C. § 102(b) Based on Plaas-Link U.S. Patent No. 5,009,861

Claims 1, 2, 8, 9, 11, 13, 17, 18, 20, 34, 36, 39, 40, 42, 45, 48 and 49 were rejected under 35 U.S.C. §102(b) as anticipated by Plaas-Link U.S. Patent No. 5,009,861. The Office Action asserted that Plaas-Link discloses a method of determining crystal forms of samples. Applicants submit that the Office Action is incorrect because Plaas-Link does not disclose determining crystal forms of a sample. The Office Action has improperly equated attempts to crystallize with

attempts to find different forms. Plaas-Link does not recognize that one might look for different crystal forms.

Plaas-Link concerns a crystallization apparatus, in particular for crystallizing proteins at zero-gravity. As recognized by the Office Action, Plaas-Link uses a crystallization apparatus to crystallize proteins from solutions inside a glass capillary so that 'unhampered observation of the crystallization progress is made possible" (col. 4, lines 14-17) when "liquid is evaporated out of the capillary tubes" (col. 4, lines 20-22). According to the Office Action, "[t]he observation of the formation of crystals has an inherited step of classification them as crystals. (sic)" However, the claims do not require classifying solids as crystals – it requires classifying solids according to form. Accordingly, the Office Action has not shown that Plaas-Link discloses all the elements of the rejected claims.

Rejection of Claims 1-3, 8, 9-11, 13, 17, 18, 20, 21, 34-40, 42, 45, 48, and 49 Under 35 U.S.C. §102(b) Based On Schuler et al. U.S. Patent No. 4,295,857

Claims 1-3, 8, 9-11, 13, 17, 18, 20, 21, 34-40, 42, 45, 48, and 49 are rejected under 35 U.S.C. §102(b) as being anticipated by Schuler et al., U.S. Patent No. 4,295,857. The Office Action asserts that Schuler teaches a process for the crystalline precipitation of chromogenes within a capillary, i.e. determining crystalline forms of the samples. The Office Action asserts that Schuler discloses preparation and observation of formation of several forms in capillaries by evaporating solvent with following spectroscopic analysis. The Office Action is incorrect in this assertion. While Schuler discloses preparing crystals of chromogene, it does not indicate any awareness or desire to screen for different solid forms of the chromogene. Schuler only desires a crystallized sample and regards the amorphous compound as unsatisfactory. Schuler does not

disclose searching or screening for different forms and therefore cannot anticipate the rejected claims.

Rejection of Claims 1, 2, 8, 9, 11, 13, 16-18, 20, 22 and 23
Under 35 U.S.C. §102(b) Based On JP 06095190

Claims 1, 2, 8, 9, 11, 13, 16-18, 20, 22 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Japanese Patent Publication No. 06095190.

JP 06095190 discloses growing an organic single crystal in a capillary. The crystal is grown by inserting a capillary in a furnace and rotating it while evaporating the solvent. The crystal is detected and "discriminated" by Raman diffusion spectroscopy.

Applicants submit that the reference does not disclose analyzing the crystal to determine its generated form or classifying the crystal according to form. The Office Action has once again improperly interpreted the claims as only requiring crystal generation.

Rejection of Claims 4, 5, and 12
Under 35 U.S.C. §103(a) Based on Schuler

Claims 4, 5, and 12 were rejected under 35 U.S.C. §103(a) over Schuler. The Office Action acknowledged that Schuler does not disclose disposing the compounds in different types of receptacles such as non-capillary receptacles or subjecting at least two different samples to different conditions during solidifying step. However, the Office Action relies on Schuler's background discussion of different conditions of evaporation, which affect the crystallization of the compound and its end form. The Office Action asserts that it would have been obvious for anyone of ordinary skill to vary the conditions of evaporation of solvents in a different way than disclosed by Schuler, namely by using capillaries along with other types of receptacles.

Applicants submit that the Office Action has failed to set forth a *prima facie* case of obviousness. The Office Action has disregarded the specific limitation in claims 4, 5, and 12 that different receptacles must be used. There is no suggestion or motivation to use different receptacles, particularly when the prior art suggests variations such as temperature and pH. (Hol, column 10, line 57, and column 11, line 25). Thus, the rejection should be withdrawn.

Rejection of Claims 6 and 7
Under 35 U.S.C. §103(a) Based On Plaas-Link

Claims 6 and 7 are rejected under 35 U.S.C. §103(a) as being unpatentable over Plaas-Link. The Office Action acknowledges that Plaas-Link does not specifically disclose placing the same sample in a plurality of capillaries but asserts that "mere duplication of parts without any new and unexpected results is within the skill in the routineer in the art".

Applicants submit that claims 6 and 7 are not merely duplicating parts. Instead, those claims define more expansive methods of searching for various forms of a compound. For that reason (as well as the earlier distinctions from Plaas-Link), the rejection should be withdrawn.

Rejection of Claims 15, 17-19, 43, 44, 46, 48, under 35 U.S.C. §103(a)
Based On Hol In View of Subbiah U.S. Patent No. 5,200,910

Claims 15, 17-19, 43, 44, 46, and 48 were rejected under 35 U.S.C. §103(a) as being unpatentable over Hol in view of Subbiah U.S. Patent No. 5,200,910. The Office Action acknowledged that Hol does not disclose synchrotron radiation as the radiation source in X-ray analysis and analyzing the sample directly in the capillary. However, the Office Action relies on Subbiah as teaching a method for modeling the electron density of a crystal by X-ray analysis of

the crystal sample placed in the capillary tube (col. 7, lines 7-12), where the X-ray radiation source is a synchrotron (col. 6, line 67).

Subbiah does not remedy the deficiencies of Hol identified above, namely that it does not disclose analyzing or classifying by form. Therefore, the rejected claims cannot be obvious.

Rejection of Claims 16, 38 and 47 Under 35 U.S.C. §103(a)
Based on Hol, Plaas-Link or Schuler
In View of Gu et al. (J.Pharmac Sci.)

Claims 16, 38 and 47 were rejected under 35 U.S.C. §103(a) as unpatentable over any of Hol, Plaas-Link or Schuler in view of Gu et al. (J.Pharmac. Sci.). The Office Action acknowledges that Hol, Plaas-Link and Schuler do not teach Raman spectroscopic analysis in their methods or discuss polymorphic forms of the compounds. However, the Office Action relies on Gu as teaching the characterization of polymorphic forms of the sample using FT Raman spectroscopy.

The Office Action improperly relies on hindsight to find a motivation to combine the references. The Office Action presumes that one already knows in Hol, Plaas-Link and Schuler that one has polymorphic compounds, and therefore he would turn to the techniques in Gu et al. The present methods provide a way to find out if a sample is a polymorphic compound. Thus, it is improper to presume that one already knows if there is a polymorphic compound present. The rejection should be withdrawn.

Rejection of Claims 24-33 and 53 under 35 U.S.C. §103(a)
Based On Hol, Plaas-Link or Schuler
In View Of Kajola (Acta Chem. Scand., Abstract)

Claims 24-33 and 53 are rejected under 35 U.S.C. §103(a) as being unpatentable over any of Hol, Plaas-Link or Schuler in view of Kajola (Acta Chem. Scand., Abstract).

The Office Action acknowledges that Hol, Plaas-Link and Schuler do not disclose centrifuging the samples in capillaries during crystallization under vacuum. However, the Office Action states that Kajola discloses:

> reaction tubes [which] are made by drawing out 10-mm glass tubing to 2 mm. diam. In these tubes the reagents are mixed and the reaction is carried out in the sealed tube. Drawing the end of the reaction tube to a fine capillary produces an effective micro-filter and the mother liquor can be centrifuged through this capillary; any crystals are left in the tube.

(Abstract). The Office Action asserts that it would have been obvious for anyone of ordinary skill to use centrifugation in Hol's, Plaas-Link's or Schuler's process of crystallization of the samples, as taught by Kajola, because Kajola teaches effectiveness of using centrifugation in separating crystals from the solvent in a capillary.

Kajola does not remedy the deficiencies of Hol, Plaas-Link and Schuler identified above. Kajola does not disclose or suggest that the sample solidified in a capillary could or should be analyzed and classified by form. Therefore, claims 24-33 and 53 are not obvious and the rejection should be withdrawn.

Rejection of Claims 55-56 under 35 U.S.C. §103(a) Based On Hol, Plaas-Link or Schuler in view of Kajola and Bringi et al. U.S. Patent No. 4,060,646

Claims 55 and 56 were rejected under 35 U.S.C. §103(a) as being unpatentable over any of Hol, Plaas-Link or Schuler in view of Kajola, as applied to claims 24-33 and 53 above, and further in view of Bringi et al. U.S. Patent 4,060,646.

The Office Action acknowledges that Hol, Plaas-Link, Schuler and Kajola do not disclose centrifuging under vacuum. However, the Office Action states that Bringi teaches fractional crystallization of food fat, wherein "separation of the crystallized fat from the mother liquor may be effected by filtration or centrifugation and accompanied with the application of vacuum or pressure". Office Action, page 8). The Office Action asserts that it would have been obvious for anyone of ordinary skill to apply vacuum during centrifugation disclosed by Bringi in Hol, Plaas-Link or Schuler/Kajola's method, because this increases the effectiveness of the centrifugation.

The Office Action is mistaken with respect to the teachings of Bringi. In Bringi, the vacuum and centrifugation are applied after the crystallization step; in contrast, in claims 55 and 56, vacuum and centrifugation are used as part of the crystallization step. Therefore the rejection is not supported by the references and should be withdrawn.

* * * * *

In view of the foregoing amendments and remarks, applicants submit that claims 1-55 are allowable. The Examiner is invited to telephone the applicants' undersigned attorney at (312) 775-8202 if any unresolved matters remain.

Please charge any fees incurred in connection with this submission to Deposit Account No. 13-0017.

Respectfully submitted,

Date: October 1, 2002

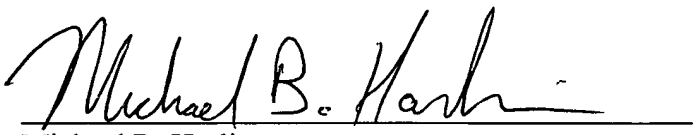

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EXHIBIT A
MARKED-UP VERSION OF CLAIMS SHOWING AMENDMENTS

12. The method of claim 1 wherein the **disposing** **[placing]** step comprises placing the sample into a receptacle selected from the group consisting of a well plate, a block with holes or pores and a sheet with holes or pores.

21. The method of claim 1 wherein said generating step produces at least one **[different]** form of the sample **that is different than a known form of the sample**.

53. A method of screening a sample, said screening method comprising the steps of:

disposing the sample on a plurality of capillary tubes;

centrifuging the plurality of capillary tubes;

solidifying the sample in the capillary tubes;

analyzing **the solids in the capillary tubes** **[said at least one form]** in a manner wherein the analytical result is indicative of **[the generated]** form; and

classifying **each of the solids according to** **[said at least one]** form.

2000

USP 24

THE UNITED STATES PHARMACOPEIA

NF 19

THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., March 9–12, 1995. Prepared by the Committee of Revision and published by the Board of Trustees

Official from January 1, 2000

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
12601 Twinbrook Parkway, Rockville, MD 20852

of the chapter and monographs and to incorporate regulatory requirements. During the revision cycle, USP adopted three monographs representing radiolabeled monoclonal antibodies. These are the first antibodies to be included in the USP.

System Suitability Tests—These tests are based on the concept that instruments, reagents, packings, conditions, procedural details, detectors, electronic accessories, and even analysts constitute a single system that is amenable to an overall test of system function. Reliable chromatographic performance, for example, may require specifications for resolution, column efficiency, peak tailing, precision of replicates, or extremes of conditions. Such tests obviate the necessity to specify a multitude of instrumental settings, model numbers, names of manufacturers, packings and lot numbers, and other physical-chemical and engineering characteristics as well as the distribution of official lots of chromatographic packings. System suitability tests, proposed from the Drug Standards Laboratory (USP-AMA-APhA) were introduced in *USP XIX* and have come into general application. Those interested in the brands of columns used during monograph development can find this information in the separate publication *Chromatographic Reagents Used in USP–NF and Pharmacopeial Forum*, which is updated bimonthly in *PF*.

Impurities—A consequence of the primacy achieved by separation science in pharmaceutical analysis is the predominance of chromatographic tests and assays. Chromatography approaches the old analytical ideal of making measurements only on purified specimens. As the resolution of an article into its components became easier, however, more attention could be paid to secondary components. There was consequently the rethinking of pharmacopeial policies since 1983. Elaboration continued in this revision cycle as well. *Other Impurities*, a requirement laid down in the *General Notices*, was added to complement existing chromatographic tests and assays. It captures alternative synthetic routes. Comparison with features of ICH guidelines show no conflict therein with compendial selection of compendial tests, assays, and limits.

Dissolution and Bioavailability—

Immediate-Release Tablets and Capsules—Dissolution requirements were added to tablet and capsule monographs starting in 1970 in response to concerns for bioavailability. Of equal significance was the recognition of the immense value of dissolution testing as a tool for quality control. Thus, equivalence in dissolution behavior was sought in light of both bioavailability and quality-control considerations throughout the last 30 years. A policy favoring a dissolution test for essentially all tablets and capsules was adopted in 1976, when the test was already a mature technology, and a more forceful policy was adopted in 1981 that was based on a presumption, or default test, First Case. *USP 24* contains *Dissolution* or *Drug release* requirements in 592 monographs.

Whenever a medically significant difference in bioavailability has been found among supposedly identical articles, a dissolution test has discriminated among these articles. Because the USP sets forth attributes of an acceptable article, such a discriminating test is satisfactory because the dissolution standard can exclude definitively any unacceptable article. Therefore, no compendial requirements for in vivo tests of bioavailability have been necessary for the public standard. The practical problem has been the obverse. Dissolution tests are so discriminating of formulation factors, factors that may only sometimes affect bioavailability of immediate-release products, that it is not uncommon for a clinically acceptable article to perform poorly in a typical dissolution test. In such cases, the Committee of Revision has been mindful of including as many acceptable articles as possible, without setting forth dissolution specifications so generous as to raise reasonable scientific concern for bioinequivalence.

Medically significant cases of bioinequivalence rest mainly on four causal factors: inappropriate particle size of an active ingredient; magnesium stearate in excess as a lubricant-glidant; coatings, especially shellac; and inadequate disintegrant. Each of these factors is reactive to dissolution testing. There is no known medically significant bioinequivalence problem with articles where 75% of an article is dissolved in water or acid at 37° in 45 minutes in the official basket or paddle apparatus operated at the usual speed, that is, USP First Case. A majority of monographs have such requirements. USP First Case performance is recognized as a reliable formulation objective in the United States and bears attention worldwide for product development where in vivo bioavailability testing is not readily available. It obviates wasteful biostudies.

Modified-Release Tablets and Capsules—USP 24 contains monographs for delayed-release and extended-release articles. Extended-release articles exist for which there are a number of successful formulations. In each case, tailor-made experiments can be made, provided that the product labeling is unambiguous and is consistent with the formulation-specific standard that applies to that article. The underlying Pharmacopeial principle is that *USP–NF* along with the product labeling are all that is required to determine the applicable standards.

PROGRAMS

USP Practitioners' Reporting Network℠ (USP PRN℠)—The USP PRN comprises three nationwide programs for reporting problems with the quality and use of drugs, and related products, and for reporting medication errors. The programs contribute significantly to the revision of compendial standards through the sharing of information reported by healthcare professionals and by industry responses to those reported problems. Each issue of *PF* lists reports received through the Drug Product Problem Reporting Program. Edited text from these reports may be requested pursuant to the USP Document Disclosure Policy.

The USP PRN publishes the *USP Quality Review*, a timely educational newsletter based on case reports received through the programs. For additional information, visit the USP PRN Web site via the USP Home Page at <**www.usp.org**> for additional information.

Open Conferences and Meetings—Consistent with the USP policy of emphasis on public participation in standards setting, open conferences and meetings are held to allow interactive examination of selected topics. These conferences were held this cycle:

May, 1995—Current Revision Issues Chicago, IL; January, 1996—Microbiological Compendial Issues Sanibel Harbour, Fort Myers, FL; February, 1996—Joint Pharmacopoeial Open Conference on Sterility/Preservatives Barcelona, Spain; July, 1996—Botanicals for Medical and Dietary Uses Washington, DC; April, 1997—USP Workshop on Microbiology and Pharmaceutical Water San Juan, Puerto Rico; May, 1997—Open Meeting on Standards for Phenylpropanolamine Hydrochloride USP Headquarters; May, 1997—Open Meeting on Packaging, Storage, and Distribution Rockville, MD; May, 1998—Open Conference Meeting on Microbiology for the 21st Century New Orleans, LA; June, 1998—Open Conference Meeting on Packaging, Storage, and Distribution Rockville, MD; August, 1998—Open Conference on Dietary Supplements Current Issues on Quality and Evidence Supporting Claims Los Angeles, CA

Conference Proceedings—There have been 25 USP conferences and meetings relevant to setting standards. Those held this cycle are listed above. Proceedings are available for many of them.

USP Fellowships—To stimulate training and research pertinent to drug standards, USPC has offered a number of fellowships to doctoral candidates. Each applicant must be sponsored by a faculty member who is a member of the current Committee of Revision or of an Advisory Panel. Awards for standards-related studies were made each year during the 1995–2000 period, bringing the program total to 159 individuals at 42 institutions.

The purpose of the USP Fellowships is to promote postgraduate research in areas related to compendial standards, thereby encouraging the education and training of Fellows in the sciences applicable to drug standardization. Recognition is also given to university faculty members elected to the USP Committee of Revision or serving on an Advisory Panel.

Visiting Scientists—A new program was started during the 1990–1995 revision cycle to increase communication and understanding among pharmacopeias and official control laboratories worldwide. USP invited scientists associated with foreign pharmacopeias or official laboratories to the USP for periods of two to four months while they studied and worked in the Standards De-

given in the manufacturer's operating instructions. If the sample must be degassed under vacuum, follow the recommendations in the individual monographs and the instructions in the operating manual for the pycnometer.

The measurement sequence above describes the procedure for the gas pycnometer shown in Figure 1. If the pycnometer differs in operation or in construction from the one shown in Figure 1, follow the operating procedure given in the manual for the pycnometer.

Repeat the measurement sequence for the same powder sample until consecutive measurements of the sample volume, V_s, agree to within 0.2%. Unload the test cell and measure the final powder weight, w. Calculate the pycnometric density, ρ, of the sample according to Equation 2.

⟨701⟩ DISINTEGRATION

This test is provided to determine compliance with the limits on *Disintegration* stated in the individual monographs except where the label states that the tablets or capsules are intended for use as troches, or are to be chewed, or are designed as modified-release dosage forms (see *Drug Release* ⟨724⟩). Determine the type of units under test from the labeling and from observation, and apply the appropriate procedure to 6 or more dosage units.

For the purposes of this test, disintegration does not imply complete solution of the unit or even of its active constituent. Complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core.

APPARATUS

The apparatus consists of a basket-rack assembly, a 1000-mL, low-form beaker, 142 to 148 mm in height and having an outside diameter of 103 to 108 mm for the immersion fluid, a thermostatic arrangement for heating the fluid between 35° and 39°, and a device for raising and lowering the basket in the immersion fluid at a constant frequency rate between 29 and 32 cycles per minute through a distance of not less than 5.3 cm and not more than 5.7 cm. The volume of the fluid in the vessel is such that at the highest point of the upward stroke the wire mesh remains at least 2.5 cm below the surface of the fluid and descends to not less than 2.5 cm from the bottom of the vessel on the downward stroke. The time required for the upward stroke is equal to the time required for the downward stroke, and the change in stroke direction is a smooth transition, rather than an abrupt reversal of motion. The basket-rack assembly moves vertically along its axis. There is no appreciable horizontal motion or movement of the axis from the vertical.

Basket-rack Assembly—The basket-rack assembly consists of six open-ended transparent tubes, each 7.75 ± 0.25 cm long and having an inside diameter of 20.7 to 23 mm and a wall 1.0 to 2.8 mm thick; the tubes are held in a vertical position by two plastic plates, each 8.8 to 9.2 cm in diameter and 5 to 7 mm in thickness, with six holes, each 22 to 26 mm in diameter, equidistant from the center of the plate and equally spaced from one another. Attached to the under surface of the lower plate is a woven stainless steel wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm. The parts of the apparatus are assembled and rigidly held by means of three bolts passing through the two plastic plates. A suitable means is provided to suspend the basket-rack assembly from the raising and lowering device using a point on its axis.

The design of the basket-rack assembly may be varied somewhat provided the specifications for the glass tubes and the screen mesh size are maintained.

Disks—The use of disks is permitted only where specified in the monograph. If specified in the individual monograph, each tube is provided with a cylindrical disk 9.5 ± 0.15 mm thick and 20.7 ± 0.15 mm in diameter. The disk is made of a suitable, transparent plastic material having a specific gravity of between 1.18 and 1.20. Five parallel 2-mm holes extend between the ends of the cylinder. One of the holes is centered on the cylindrical axis. The other holes are centered 6 mm from the axis on imaginary lines perpendicular to the axis and parallel to each other. Four identical trapezoidal-shaped planes are cut into the wall of the cylinder, nearly perpendicular to the ends of the cylinder. The trapezoidal shape is symmetrical; its parallel sides coincide with the ends of the cylinder and are parallel to an imaginary line connecting the centers of two adjacent holes 6 mm from the cylindrical axis. The parallel side of the trapezoid on the bottom of the cylinder has a length of 1.6 mm, and its center lies at a depth of 1.8 mm from the cylinder's circumference. The parallel side of the trapezoid on the top of the cylinder has a length of 9.2 mm, and its center lies at a depth of 2.6 mm from the cylinder's circumference. All surfaces of the disk are smooth. If the use of disks is specified in the individual monograph add a disk to each tube, and operate the apparatus as directed under *Procedure*.

PROCEDURE

Uncoated Tablets—Place 1 tablet in each of the six tubes of the basket and operate the apparatus, using water maintained at 37 ± 2° as the immersion fluid unless otherwise specified in the individual monograph. At the end of the time limit specified in the monograph, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Plain Coated Tablets—Apply the test for *Uncoated Tablets*, operating the apparatus for the time specified in the individual monograph.

Delayed-release (enteric coated) Tablets—Place 1 tablet in each of the six tubes of the basket and, if the tablet has a soluble external coating, immerse the basket in water at room temperature for 5 minutes. Then operate the apparatus using simulated gastric fluid TS maintained at 37 ± 2° as the immersion fluid. After 1 hour of operation in simulated gastric fluid TS, lift the basket from the fluid, and observe the tablets: the tablets show no evidence of disintegration, cracking, or softening. Operate the apparatus, using simulated intestinal fluid TS maintained at 37 ± 2° as the immersion fluid, for the time specified in the monograph. Lift the basket from the fluid, and observe the tablets: all of the tablets disintegrate completely. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Buccal Tablets—Apply the test for *Uncoated Tablets*. After 4 hours, lift the basket from the fluid, and observe the tablets: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Sublingual Tablets—Apply the test for *Uncoated Tablets*. Observe the tablets within the time limit specified in the individual monograph: all of the tablets have disintegrated. If 1 or 2 tablets fail to disintegrate completely, repeat the test on 12 additional tablets: not less than 16 of the total of 18 tablets tested disintegrate completely.

Hard Gelatin Capsules—Apply the test for *Uncoated Tablets*. Attach a removable wire cloth, which has a plain square weave with 1.8- to 2.2-mm mesh apertures and with a wire diameter of 0.60 to 0.655 mm, as described under *Basket-rack Assembly*, to the surface of the upper plate of the basket-rack assembly. Observe the capsules within the time limit specified in the individual monograph: all of the capsules have disintegrated except for fragments from the capsule shell. If 1 or 2 capsules fail to disintegrate completely, repeat the test on 12 additional capsules: not less than 16 of the total of 18 capsules tested disintegrate completely.

Soft Gelatin Capsules—Proceed as directed under *Hard Gelatin Capsules*.

⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or

disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. For hard gelatin capsules that do not conform to the *Dissolution* specification, repeat the test as follows. Where water is not specified as the *Medium* in the individual monograph, the same *Medium* specified in the monograph may be used with the addition of not more than 3.2 g of purified pepsin having an activity of 800 to 2500 units per mg of protein, or not more than 5 g of pancreatin, per 1000 mL of *Medium*, as appropriate. Pepsin is added to acidic media, while pancreatin is appropriate for media at or above a pH of 6.8. Where the monograph specifies water as the *Medium*, a second medium of either 0.1 *N* hydrochloric acid with pepsin or pH 6.8 phosphate buffer with pancreatin, depending on the drug solubility, may be used with the concentration of pepsin or pancreatin being the same as above.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating)*. *USP Salicylic Acid Tablets RS (Dissolution Calibrator, Nondisintegrating)*.

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 liter, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 liters, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 liters, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%.

Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 μm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity that may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

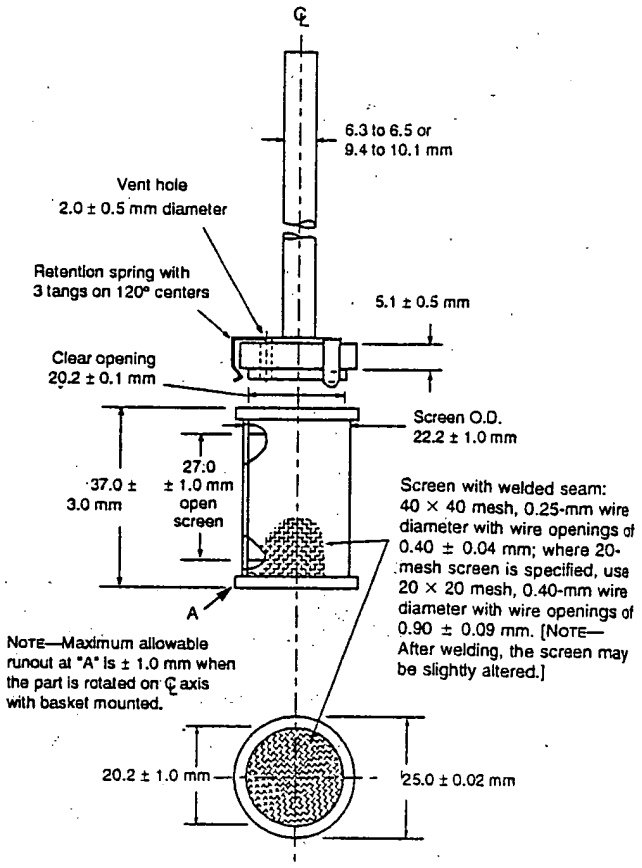

Fig. 1. Basket Stirring Element.

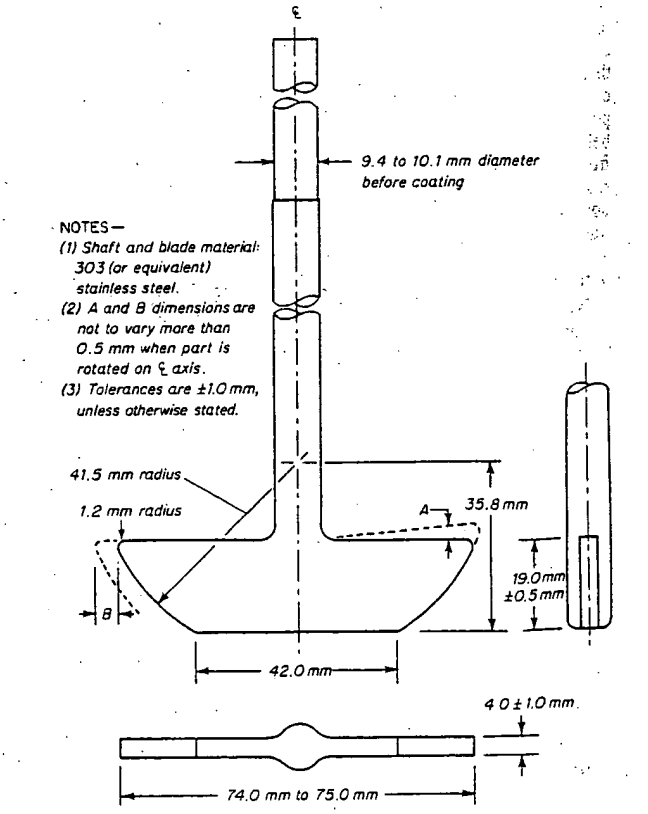

Fig. 2. Paddle Stirring Element.

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type* and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type*, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph. [NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* (±1%) in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall. [NOTE—Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation. Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.] Perform the analysis as directed in the individual monograph.[4] Repeat the test with additional dosage form units.

If automated equipment is used for sampling and the apparatus is modified, validation of the modified apparatus is needed to show that there is no change in the agitation characteristics of the test.

Where capsule shells interfere with the analysis, remove the contents of not less than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium*. Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Procedure for a Pooled Sample for Capsules, Uncoated Tablets, and Plain Coated Tablets—Use this procedure where *Procedure for a Pooled Sample* is specified in the individual monograph. Proceed as directed under *Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets*. Combine equal volumes of the filtered solutions of the six or twelve individual specimens withdrawn, and use the pooled sample as the test solution. Determine the average amount of the active ingredient dissolved in the pooled sample.

Interpretation—

Unit Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content; the 5%, 15%, and 25% values in the Acceptance Table are percentages of the labeled content so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1 + S_2) is equal to or greater than Q, and no unit is less than Q − 15%.
S_3	12	Average of 24 units (S_1 + S_2 + S_3) is equal to or greater than Q, not more than 2 units are less than Q − 15%, and no unit is less than Q − 25%.

Pooled Sample—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the pooled sample conform to the accompanying Acceptance Table for a Pooled Sample. Continue testing through the three stages unless the results conform at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content.

Acceptance Table for a Pooled Sample.

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is not less than Q + 10%.
S_2	6	Average amount dissolved (S_1 + S_2) is equal to or greater than Q + 5%.
S_3	12	Average amount dissolved (S_1 + S_2 + S_3) is equal to or greater than Q.

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 μm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause adsorption of the active ingredient or contain extractable substances that would interfere with the analysis.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

Method I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper insulating board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the insulating material has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.